

REMARKS

Claims 1 to 22 as presented with applicants' paper of January 09, 2009, are currently pending. Claim 1 is the sole independent claim, and Claims 2 to 22 depend either directly or indirectly upon Claim 1.

As provided in Claim 1, applicants' invention pertains to a procedure for producing a solid dosage form which comprises

- (i) forming a moldable cohesive composition comprising
 - (a) from 50 to 99.4% by weight of at least one crosslinked, non-thermoplastic carrier;
 - (b) from 5 to 30% by weight of at least one adjuvant selected from the group of thermoplastic polymers, liquids, sugar alcohols, sugar alcohol derivatives and solubilizers, and
 - (c) from 0.1 to 30% by weight of at least one active ingredient,by heating at a temperature at or above the softening point of the adjuvant, but at least 70°C, in a multi-screw extruder to obtain a moldable composition, and
- (ii) subsequently cooling the moldable composition.

The Examiner stated in Nos. 6., 7. and 8. on pages 2 and 3 of the Office action that applicants' arguments presented on January 09, 2009, concerning the previous rejections of Claims 1 to 20 under 35 U.S.C. §103(a) "*have been fully considered and are found persuasive. Therefore, the rejection of 07/09/08 is maintained*" (*emphasis added*). Clarification is respectfully solicited. To the extent the respective rejections have not been withdrawn by the Examiner, applicants herewith incorporate their paper of January 09, 2009, by reference.

The Examiner newly rejected Claims 1 to 4, 6 to 8, 10 to 19, 21 and 22 under 35 U.S.C. §103(a) as being unpatentable in light of the teaching of *Klimesch et al.* (US 5,073,379) when taken in view of the disclosure of *Thacharodi et al.* (EP 0 960 620). The Examiner acknowledged that *Klimesch et al.* failed to teach the utilization of high amounts of a crosslinked, non-thermoplastic carrier, but alleged that a person of ordinary skill would have employed a "*composition with a high percentage (10 to 98%) of a pharmaceutically acceptable carrier such as a cross-linked polyvinylpyrrolidone (...), as taught by*" *Thacharodi et al.* in the process of *Klimesch et al.*, e.g., because:
1) combining prior art elements according to known methods to yield predictable results would

have been obvious to one of ordinary skill; and

- 2) it is apparent from the references that one of ordinary skill in the art would have had a reasonable expectation of success.

For the following reasons, applicants respectfully disagree.

The teaching of *Klimesch et al.* pertains to a process of preparing a solid pharmaceutical form by extruding a polymer melt containing an active ingredient and subsequently forming the still plastic extrudate between a belt and a roller or two belts. The respective polymer melt is based on a certain polymeric binder which is required to “soften or melt at from 50 to 180°C, preferably from 60 to 130°C, so that the mass is extrudable. The glass transition temperature of the mixture must thus in any case be less than 180°C, preferably less than 130°C.”¹⁾ Notably, also, *Klimesch et al.* limit the total amount of conventional auxiliaries, e.g., including any disintegrants, which may be present in the mixture to up to 100% by weight, based on the polymeric binder,²⁾ i.e., the weight ratio of auxiliaries to binder is at most 1:1.

A person of ordinary skill in the art will readily appreciate that the cross-linked, non-thermoplastic carrier which is employed in accordance with applicants’ procedure cannot be softened or molten under the conditions required by *Klimesch et al.*, and that cross-linked PVP which is mentioned in both references as a disintegrant³⁾ decomposes upon heating prior to melting. Accordingly, no glass transition temperature can be measured for cross-linked, non-thermoplastic PVP. The enclosed copy of a publication of *Saavedra et al.*, for example, states: “The measured decomposition temperature was 367°C, so T_g [the glass transition temperature] for crosslinked PVP could be higher than this value.”⁴⁾ As pointed out in the foregoing, *Klimesch et al.* require that the glass transition temperature of the extruded mixture must in any case be less than 180°C and preferably less than 130°C. On the basis of the information which is provided by *Klimesch et al.*, it is therefore not deemed to be obvious to a person of ordinary skill in the pertinent art to increase the amount of any non-thermoplastic material(s) beyond the at most 1:1 auxiliaries to polymeric binder ratio which is taught in the primary reference. In fact, bearing in mind that cross-linked PVP is non-thermoplastic, and as such will not soften or melt at from 50 to 180°C as is required by *Klimesch et al.*, a person of ordinary skill in the art could not even reasonably expect that a composition wherein the ratio of non-thermoplastic carrier to any thermoplastic binder is

1) Col. 3, indicated lines 24 to 29, of *US 5,037,379*; *emphasis added*.

2) C.f., col. 4, indicated lines 30 to 40, of *US 5,073,379*.

3) C.f., e.g., col. 6, indicated lines 57 to 58, of *US 5,073,379*, and page 4, indicated line 55, of *EP 0 960 620*.

4) Para. 2 of “3. Results and Discussion” on page 282, lines 5 and 6, of *Saavedra et al.*

at least 1.67:1⁵⁾ even may be extrudable since the extrudability of the composition is, according to *Klimesch et al.* clearly linked to the pertinent amounts and properties of the thermoplastic binder. For the same reason, the results of an extrusion of a composition comprising considerably and distinctly higher amounts of non-thermoplastic carrier cannot be deemed to have been predictable at the time applicants made their invention.

The information which is given in the disclosure of *Thacharodi et al.* is not deemed to render the result of such an extrusion predictable, or to suggest or imply that such an extrusion may reasonably be expected to be successful. *Thacharodi et al.* employ polymers which comprise vinylpyrrolidone monomeric units as stabilizing excipients for substituted pyridylsulfinyl benzimidazoles.⁶⁾ In this context it is thus the presence of the pyrrolidone moieties which determine the suitability of the polymer for the purposes of *Thacharodi et al.*'s disclosure and not the thermoplastic properties which are required in the context of *Klimesch et al.*'s process. In fact, in accordance with the disclosure of *Thacharodi et al.* it is not even of concern whether the respective ingredients form a moldable composition since the ingredients are to be mixed to form a blend or granules which blend or granules are to be placed into capsules.⁷⁾

The Examiner alleged that it would have been obvious "*to use a process for the preparation of solid pharmaceutical forms by extruding a polymer melt containing the active compound and forming the still plastic extrudate between a belt and a roller or two belts, as taught by Klimesch, combine it with the process of making a granular pharmaceutical composition with a high percentage (10 to 98%) of a pharmaceutically acceptable carrier such as cross-linked polyvinylpyrrolidone (Kollidon CL-M), as taught by Thacharodi, and produce the instant invention.*"⁸⁾ However, to make a granular composition as is disclosed by *Thacharodi et al.* is in stark contrast to providing a polymer melt, and to forming a plastic mixture, as is required in accordance with *Klimesch et al.*'s process. Clearly, *Klimesch et al.* convey that the initial plasticity and formability of the extruded mixture is an indispensable part of the success of the process when stating: "*To ensure reliable transport of the extrudate and to avoid breaking off downstream of the die ...*" *Klimesch et al.*, therefore, strongly suggest that it is pertinent that the extrudate at least initially be of cohesive consistency rather than granular. This, again, would have dissuaded a person of ordinary skill in the art from employing the process of *Klimesch et al.* for processing the mixture of *Thacharodi*

5) Corresponding to 50% by weight of applicants' component (a) and 30% by weight of applicants' component (b).

6) E.g., page 2, indicated lines 5 to 7, and page 3, indicated lines 2 to 4, of *EP 0 960 620*.

7) E.g., page 5, indicated lines 20 to 24, of *EP 0 960 620*.

8) Office action page 6, line 18, to page 7, line 3, *emphasis added*.

et al. as such a person could not reasonably predict the result of such a modified process, nor was there any reasonable expectation that such a process would be successful.

It is therefore respectfully urged that the procedure defined in applicants' Claim 1 cannot be deemed to be rendered unpatentable under Section 103(a) by the teaching of *Klimesch et al.* when taken in view of the disclosure of *Thacharodi et al.*, and the same applies where the subject matter of applicants' Claims 2 to 22 is concerned.⁹⁾ Favorable reconsideration of the Examiner's position and withdrawal of the rejection of Claims 1 to 4, 6 to 8, 10 to 19, 21 and 22 for that reason is respectfully solicited.

Further, the Examiner newly rejected Claim 5 under 35 U.S.C. §103(a) as being unpatentable in light of the teaching of *Klimesch et al.* when taken in view of the disclosures of *Thacharodi et al.* and of *Endicott et al.* (US 3,087,860). The Examiner acknowledged that the combination of *Klimesch et al.* and *Thacharodi et al.* failed to teach the utilization of sugar alcohols as adjuvants, but alleged that a person of ordinary skill would have been motivated to introduce such adjuvants because of the disclosure of *Endicott et al.* However, the disclosure of *Endicott et al.* is unsuited to render the result of a modification of *Klimesch et al.*'s process on the basis of the disclosure of *Thacharodi et al.* predictable, or to supplement the necessary reasonable expectation of success for such a modification. The mere fact that *Endicott et al.* show sugar alcohols to be excipients or adjuvants for pharmaceutical compositions is not deemed to be sufficient to render the subject matter of applicants' Claim 5 as a whole obvious within the meaning of Section 103(a). It is therefore respectfully requested that the respective rejection be withdrawn. Favorable action is respectfully solicited.

Additionally, the Examiner newly rejected Claims 9 and 20 under 35 U.S.C. §103(a) as being unpatentable in light of the teaching of *Klimesch et al.* when taken in view of the disclosures of *Thacharodi et al.* and of *Goertz et al.* (US 4,801,460). Here, the Examiner acknowledged that the combination of *Klimesch et al.* and *Thacharodi et al.* failed to teach comminuting and compressing the cooled extrudate to the dosage form, but alleged that a person of ordinary skill would have been motivated to do so by the disclosure of *Goertz et al.* However, nothing in the disclosure of *Goertz et al.* suggests or implies that a composition comprising non-thermoplastic, crosslinked

9) If an independent claim is non-obvious under 35 U.S.C. §103, then any claim depending therefrom is non-obvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

carriers in the amounts mandated by applicants' claims may be extruded successfully. In fact, similar to the teaching of *Klimesch et al.*, *Goertz et al.* limit the total amount of pharmaceutical auxiliaries, including i.e. disintegrants, to 100% based on the amount of polymer binder.¹⁰⁾ As such, the disclosure of *Goertz et al.* is also not deemed to be suited to render the result of a modification of *Klimesch et al.*'s process on the basis of the disclosure of *Thacharodi et al.* predictable, or to supplement the necessary reasonable expectation of success for such a modification. The mere fact that *Goertz et al.* mention cold-face cutting and pressing the granules into tablets cannot be considered sufficient to render the subject matter of applicants' Claims 9 and 20 as a whole obvious within the meaning of Section 103(a). It is therefore respectfully requested that the respective rejection be withdrawn. Favorable action is respectfully solicited.

10) C.f., col. 5, indicated lines 38 to 48, of *US 4,801,460*.

Photoacoustic evaluation of molecular weight and crosslinking effects on thermal diffusivity in Poly(N-vinyl-2-pyrrolidone)

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Abstract. The thermal diffusivity of Poly(N-vinyl-2-pyrrolidone) (PVP) samples was investigated using open photoacoustic cell technique (OPC) as function of molecular weight and crosslinking. Differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and X ray diffraction (XRD) techniques were also used to the PVP characterization.

1. INTRODUCTION

Poly(N-vinyl-2-pyrrolidone) (PVP) is one of the most frequently investigated linear vinyl polymers for its medical and biological applications [1]. PVP is a white and hygroscopic powder, which has been used in a very large number of applications due to its remarkable properties (amphiphilic character, complexing ability, biocompatibility, etc). According to the structural formula, the monomer unit have an amphiphilic character because it contains a highly polar amide group conferring hydrophilic and polar-attracting properties, and also apolar methylene and methine groups in the backbone and the ring, conferring hydrophobic properties [2]. In contrast with most of polymers, it is readily soluble both in water and in a large number of organic solvents. On the other hand, this polymer is insoluble in common esters, ethers, hydrocarbons and ketones.

The thermal diffusivity is an important physical parameter that is strongly dependent on the compositional and structural variables of the polymeric material. In this note, we report thermal properties of the PVP as function of molecular weight and crosslinking. We used the open photoacoustic cell (OPC) technique to measure the effective thermal diffusivity (α_{eff}) of PVP as function of molecular weight and crosslinking. It is well known that the photoacoustic methods had been successfully applied to the thermal characterization of polymers [3-6]. The characterization of thermophysical properties of the PVP was also performed by using Differential Scanning Calorimetry (DSC), Thermogravimetric Analysis (TGA) and X ray Diffraction analysis (XRD).

2. EXPERIMENTAL

PVP powder samples with different weight average molecular weights \bar{M}_w (24.000, 40.000, 55.000, 1.300.000 [$\frac{g}{mol}$]) and crosslinking were obtained from AldrichTM. Disk-plate like samples were made by pressing PVP powders (~ 470 [MPa]). The effective thermal diffusivity (α_{eff}) measurement setup considers the well known OPC technique. The mechanically modulated light from 100 [mW] Ar ion laser is focused onto the sample. The sample was mounted on top of a commercial electret microphone

and sealed with vacuum grease. To ensure optical opacity of the samples, a thin Al foil was glued with thermal paste to the illuminated surface. The PA signal from the microphone was lock-in amplified and its amplitude and phase were digitally recorded as function of the modulation frequency f . The α_{eff} was obtained by fitting PA amplitude signals in the thermally thick regime, i.e. for ranges of f where $l_s \gg \mu_s$, with l_s thickness and $\mu_s = \sqrt{\frac{\alpha_{eff}}{\pi f}}$ the thermal diffusion length of the sample [6, 7].

The TGA and DSC analysis were done in PVP powder samples, using a simultaneous thermal analyser TGA/DSC Polymer Laboratories STA 625. Samples (2 – 3 [mg]) were placed inside aluminium pans and heated under flowing nitrogen (41 $\frac{mL}{min}$) ranging from 25 to 550 [$^{\circ}C$], at 10 $\frac{^{\circ}C}{min}$. So, the corresponding thermograms and thermal decomposition profiles were obtained, which are characteristic descriptions of each polymer. In addition, the crystallinity degree (%) of PVP samples was calculated from XRD analysis. The X-ray diffractograms were performed with a Siemens D500 diffractometer with Cu K_{α} line.

3. RESULTS AND DISCUSSION

The figure 1 shows the measured properties of PVP samples as function of \bar{M}_w . It can be seen small values of α_{eff} at small \bar{M}_w values. After that there is a rise in the α_{eff} as the \bar{M}_w become larger. On the other hand, PA measurements of α_{eff} display the same \bar{M}_w dependence when compared with T_g values obtained from DSC. This can be interpreted in terms of specific heat because small α_{eff} value could mean large specific heat values. While heating samples the internal energy of the system increases and this energy can be used in other molecular events such as internal conformational transitions. The detectable conformational changes occur at the T_g , where the polymer has gained enough internal energy to rotate C – C bonds in the macromolecule backbone. For low \bar{M}_w this changes are allowed at lower T which is reflected on a decreasing T_g .

As the crosslinked PVP can not be expressed in terms of \bar{M}_w , its properties are shown in the table 1. The T_g value for crosslinked PVP is not observed. In fact, the crosslinking phenomena work against the conformational transitions, so then T_g increases. When crosslinks are large enough the required motions to reach the glass temperature regime can never be achieved and the polymer will degrade before reaching T_g [8]. The measured decomposition temperature was 367 $^{\circ}C$, so T_g for crosslinked PVP could be higher than this value. This observation also agrees with an expected high α_{eff} value, as we discussed above. However, the relative increase of α_{eff} can be associated to the porosity of compact PVP samples too. Scanning electron microscopy (SEM) shows polymeric matrix containing domains of air inclusions within the compacts [Fig. 2]. The α_{eff} depends on both PVP and enclosed air. It had been described that the thermal diffusivity of air-filled porous material is modified with porosity [7, 9, 10], since the room temperature air thermal diffusivity is relatively high, $\alpha_{air} = 21 \left[\frac{mm^2}{s} \right]$. Regardless the porosity constant effect on PVP compact samples, we can qualitatively consider the observed α_{eff} dependence on \bar{M}_w for this kind of porous samples. In conclusion, the inspected properties of PVP are a function of composition and structure as well as \bar{M}_w and crosslinking.

Acknowledgements

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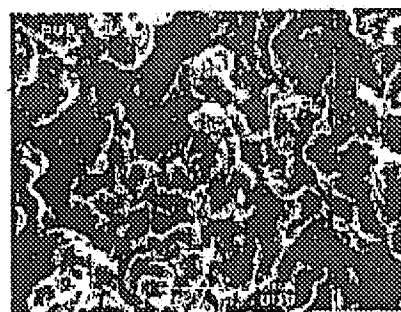
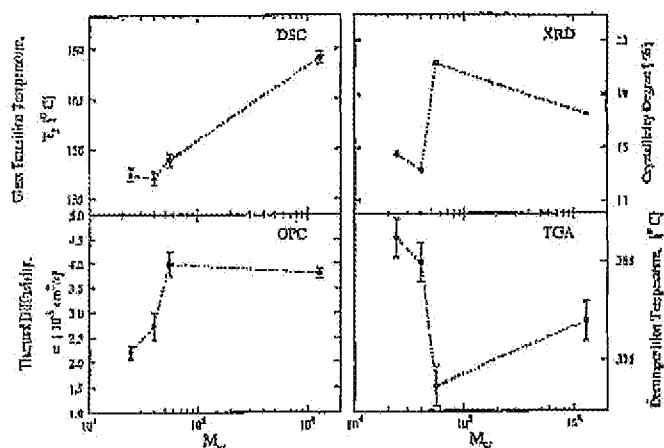


Figure 1. Thermal and Physical properties of PVP as function of molecular weight M_w : Effective thermal diffusivity α_{eff} (left bottom), Glass transition temperature T_g (left top), Decomposition temperature (right bottom) and Crystallinity degree (right top)

Figure 2. SEM image of PVP crosslinked.

Table 1. Measured Properties of PVP crosslinked

Effective Thermal Diffusivity	$8.64 \pm 2.51 \left[\frac{\text{mm}^2}{\text{s}} \right]$
Decomposition Temperature	$367^\circ\text{C} \pm 5^\circ\text{C}$
Crystallinity Degree	13.9 %

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